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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/838,486	04/07/97	BAEKKESKOV S	02307U-3122

HM11/0428

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EXAMINER	
TUNG, M	

ART UNIT	PAPER NUMBER
1644	6

DATE MAILED: 04/28/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/838,486	Applicant(s) Baekkeskov
	Examiner Mary Tung	Group Art Unit 1644

☒ Responsive to communication(s) filed on *3/16/98* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *31-42* is/are pending in the application.

Of the above, claim(s) *38-42* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *31-37* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Mary Tung, Ph.D., Group Art Unit 1644, Group 1640, Technology Center 1600.

DETAILED ACTION

2. Claims 31-42 are pending in this application.

3. If applicant desires priority under 35 U.S.C. 120(a-d) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

4. The specification should be amended to reflect all continuing data relevant to the instant application. The following wording is suggested: "This application is a divisional of serial number 08/452,053, which is a continuation of serial number 08/174,550, now U.S. Patent No. 5,512,447, which is a continuation of serial number 07/756,207, now abandoned, which is a continuation of serial number 07/579,007, now abandoned."

Information Disclosure Statement

5. References (AN, AS, AZ, BA, BN, and BT), crossed out on the PTO Form 1449, filed 4/8/97 have not been considered because the applicant has not supplied said references. References (AN, AS, AZ, BA, BN, and BT), have not been considered because said references cannot be found in the parent application, Serial Number 07/579,007.

Election/Restriction

6. Claims 38-42 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 5.

Specification

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Methods for the Treatment of Type I Diabetes Using Glutamic Acid Decarboxylase."

8. The use of the trademarks such as "IMMOBILON," page 27, line 17, "SEPHAROSE," page 29, line 4, and so on, of the specification has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

9. Each letter of the trademarks must be capitalized. *See MPEP 608.01(V)* and *Appendix 1.*

10. The disclosure is objected to because of the following minor informalities: The word "individuals" is misspelled on page 21, line 12. Figure 8 is not referred to in the disclosure on page 37, lines 1-23. Appropriate action is required.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 31-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

13. The goal of peptide immunotherapy of T-cell-mediated autoimmunity is to induce anergy in self reactive T cells. Therefore, the pathologies of autoreactive T cells in autoimmunity can be blocked by using the appropriate autoantigen or autoantigen-derived peptides (see Tisch, et al., (X), page 437, col. 1, in particular). However, the effectiveness of this therapy hinges on several factor: one is whether the therapy can be used to treat an ongoing autoimmune response or whether it is useful only in preventing the disease. Typically, an autoimmune disease is diagnosed at the time of onset when significant tissue damage has already occurred. The onset of IDDM is not predicable and therefore, prophylaxis of these diseases is not currently possible; currently, therapy is initiated in these conditions only after the onset of disease symptoms. Furthermore, Tisch et al., (X) teach that treating an ongoing T-cell-mediated autoimmunity by administering an antigen peptide may have an immunizing effect and exacerbate the

disease condition ((X), page 437, column 3, in particular). How the antigen is administered is also a key factor in determining whether an immunogenic or tolerogenic response is induced. The duration of the toleragenic effect is an additional factor. Frequent treatment over a prolonged period of time may result in unforseen immunological complications. Furthermore, the applicant discloses on page 20, lines 16-19, that "care should be taken that administration of the pharmaceutical compositions of the present invention does not potentiate the autoimmune response." There is a lack of guidance in the specification as to how the potentiation of the autoimmune response would be prevented using the instant invention. Additionally, the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS, IDDM and rheumatoid arthritis, in which there are responses to several antigens ((X), see page 437, col. 2 ¶ 3 and bridging over to col. 3, ¶ 4). Additionally, Lernmark (W) teaches that "The mechanisms of GAD65-induced protection of spontaneous diabetes is critical to our understanding of autoimmune diabetes. Further experiments also extended to the spontaneously diabetic BB rat are warranted to determine the mechanism of protection, especially as other investigators have not found the published procedures to be easily reproducible." ((W), see page 274, col. 2, paragraph 1, in particular). Additionally, Harrison (V) teaches that "Insulin and GAD are strong candidate toleragens for the prevention of human IDDM. However, caution should be exercised with GAD because, unlike insulin, it is not β cell specific and is found in high concentrations in the brain as well as in peripheral tissues other than islets. Without further animal studies and knowledge of the GAD epitopes that elicit T cell reactivity unique to human β cells, it would seem unwise to manipulate immunity to this widely distributed key enzyme. For the present, insulin (or proinsulin) is the only islet antigen that, both on scientific and ethical grounds, justifies therapeutic application to humans at risk of IDDM." ((V), see page 724, col. 2, paragraph 2, in particular). Applicant has provided only in vitro experiments demonstrating the identity of GAD in rat islets of Langerhans and in rat brain, and anti-GAD antibodies in the sera of patient with IDDM and stiff man syndrome, to demonstrate operability of the claimed polypeptide. Since human and rats display different major histocompatability complex haplotypes and applicant has given no guidance as to how their peptide specific therapy would overcome autoreactive T cell escape mechanisms in humans or whether the peptide would induce autoimmunity or tolerance, it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

14. Further, there is no guidance how to achieve the recited inhibition of the development of IDDM wherein the GAD is coupled to an immunoglobulin or a lymphoid cell as recited in claims 32, 33 and 36. Kalden et al., teach on page 336, col. 1, paragraph 2, that immunoglobulin therapy may regulate autoimmunity through the idiotype/antiidotype network or by inhibiting T cell-dependent B cell differentiation, however, placebo-controlled double-blind studies are still missing and that the

management of autoimmune disorders with antibodies is still an unsolved problem. Additionally, on page 352, col. 3, Kalden teaches that clinical efficacy can only be judged in relatively large clinical trials due to possible variations in antigen-binding characteristics, variations in the dose and timing of the monoclonal antibody. The applicant provided the Braley-Mullen reference on page 20 of the specification as an example of using antigen coupled to a lymphoid cell to induce tolerance. However, Braley-Mullen teaches on page 164 that it is not possible to demonstrate the presence of Ts. cells in tolerant spleen cells unless the cells undergo a second activation step *in vitro* or the tolerant mice are pretreated with the cells. This suggests that another cell type present in the S3-SC mice used by Braley-Mullen can interfere with the expression or activation of S3-specific Ts cells. (see paragraph 2, in particular). Therefore, it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

15. The specification fails to provide guidance as to how to determine which amino acid fragments would have the acitvity recited herein. The specification also fails to provide guidance as to how to modify the intact enzyme that would decrease binding to an associated T-cell receptor while maintaining binding to the major histocompatability complex, whereby the cellular immune response is inhibited. Detailed information regarding the structural and functional requirements of the GAD protein is lacking. Therefore, predicting which amino acid fragments or modified enzyme would maintain function is well outside the realm of routine experimentation; thus a skilled artisan would require guidance, such as information regarding the location, size, and sequence of deletions and modifications would be required to obtain modified fragments or modified enzyme that would have the recited inhibitory function. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention.

16. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 31-34 are rejected under *35 U.S.C. § 112*, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

19. It is unclear what is meant by the term "preselected dosage" in claim 31.

20. Claim 32 recites the limitation "tested" in line 24. There is insufficient antecedent basis for this limitation in the claim.

21. Claim 33 contains the following informality: "major histocompatability complex" should be defined in the claims the first time the term is recited. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 31 and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Atkinson ((AM), Patent # WO 90/07117).

23. The '117 patent teaches the administration of 64K proteins or hybrid 64K proteins to prevent or slow the onset of IDDM (see page 7, lines 5-10, in particular) and a composition containing the 64K antigen, (see the title and page 31, lines 10-16, and claims 15-17, in particular). The 64K protein associated with IDDM has subsequently been identified as being glutamic acid decarboxylase (see Baekkeskov, et al. (AT), Nature, 347:151-156, 1990). The method of using a preselected dosage of GAD, recited in claim 31 is inherent in clinical therapies: the dosage is always preselected prior to administration to a patient. The term "comprising" recited in claim 35, is interpreted as including the GAD protein or any other constituent. Therefore, the reference teachings anticipate the claimed invention.

24. Claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by Chang and Gottlieb (AX).

25. Chang and Gottlieb (AX) teach the use of GAD in a pharmaceutical preparation by immunizing a mouse with purified rat brain GAD in a composition comprising GAD and Freund's adjuvant (see page 2124, col. 2, paragraph 3, in particular).

Claim Rejections - 35 USC § 103

26. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

27. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

28. Claims 31, 32, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atkinson ((AM), Patent# WO 90/07117) in view of Dorf (U) and Huston ((A), US Patent #5,258,498).

29. The '117 patent has been discussed, *supra*. The claimed invention differs from the reference teaching only by the recitation of a method wherein the GAD or fragment thereof is coupled to an immunoglobulin or lymphoid cell. To generate a class of novel biosynthetic, bi or multi functional proteins that comprise antigen binding sites which can be used as a bioactive effector molecule, the '498 patent teaches an antibody binding site which are linked to a protein having biological activity, such as an enzyme ((A), see col. 6, lines 53-69, in particular). In this aspect, the invention provides "self-targeted" proteins which have a bioactive function and which deliver that function to a locus determined by the binding site's specificity. Dorf reviews the use of antigen-coupled syngeneic splenic adherent or nonadherent cells to induce antigen-specific non-responsiveness (see page132, paragraph 3, in particular). One of ordinary skill in the art at the time the invention was made would have been motivated to couple GAD to an immunoglobulin as taught by Huston (A) or a lymphocyte as taught by Dorf (U), in the method for inhibiting the development of IDDM as described by Atkinson, discussed *supra,* in order to provide "self-targeted" proteins which have a bioactive function (to induce self-tolerance) and which deliver that function to a locus determined by the binding site's specificity ((the β cells), see the '498 patent, col. 6, lines 53-69). From

the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

30. Claims 33 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atkinson ((AM), Patent# WO 90/07117), in view of Dorf (U), and Huston ((A), US Patent #5,258,498) as applied to claims 31, 32, 35 and 36 above and in further view of Wraith (Y).

31. The '117 patent has been discussed, *supra*. The claimed invention differs from the reference teaching only by the recitation of a method wherein the GAD or fragment thereof has been modified (claims 33 and 37) to decrease binding to an associated T-cell receptor while maintaining binding to the major histocompatability complex, whereby the cellular immune response is inhibited. To inhibit the development of the autoimmune disease, autoimmune encephalomyelitis in mice, Wraith (Y) teaches the use of analogs of the autoantigen, myelin basic protein (see the abstract, in particular) and to design synthetic peptides that will bind with high affinity to the major histocompatability complex, but will not activate Th cells ((Y), via the T cell receptor, see page 247, col. 2, paragraphs 2 and 3, in particular). Wraith also teaches a method of determining the dose of peptide needed to activate T cells (see Figure 1, in particular). One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the autoantigen GAD, for the autoantigen myelin basic protein, taught by Wraith for the prevention of IDDM, to inhibit the development of the autoimmune disease. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

32. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

33. Papers related to this application may be submitted to Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). THE CM1 FAX CENTER TELEPHONE NUMBER IS (703) 305-3014 or (703) 308-4242.

34. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mary Tung whose telephone number is (703)308-9344. The Examiner can normally be reached Monday through Friday from 8:30 am to 5:30 pm. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1640 receptionist whose telephone number is (703) 308-0196.

April 27, 1998
Mary B. Tung, Ph.D.
Patent Examiner
Group 1640

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
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